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ABSTRACT

This report covers a summary of 300 animal experiments during profound hypothermia which stresses (1) the acceptable animal survival rate, (2) the favorable metabolic state afforded by this technique and (3) the protective action of profound hypothermia against even severe oxygen deprivation. The technique of profound hypothermia induced and controlled with a pump oxygenator has been shown to be feasible by these studies and has now been widely accepted for clinical application. It has become increasingly evident that, though long periods of circulatory arrest can be achieved, flow of oxygenated blood ought not to be stopped unless the operation demands it. The basis for this statement rests upon the observations that oxygen is utilized during profound hypothermia. There are few cardiac operations where prolonged circulatory arrest is ever needed.

PUBLICATION REVIEW

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EXPERIMENTAL STUDIES ON PROFOUND HYPOTHERMIA INDUCED AND REVERTED WITH A PUMP OXYGENATOR

SECTION 1. INTRODUCTION

The possibility of the clinical use of profound hypothermia induced and controlled with a pump oxygenator was first suggested to the authors by the reports of Gollan (1954). Some of our laboratory studies and clinical experience on this subject have already been published (Lesage et al, 1959; 1960; 1961; Sealy et al, 1958; In press; Young et al, 1959). Now many laboratories have reported observation on profound hypothermia, some unfavorable but others confirming our findings of the salutary effect of this modality (Bjork and Hultquist, 1960; Drew et al, 1959; Gordon et al, 1960; Lim et al, 1961; Overbeck, 1961; Shields and Lewis, 1959; Urschel and Greenberg, 1960). Most studies, whether showing favorable or unfavorable metabolic findings (Ellison et al, 1960; 1961; Krasna et al, 1961; Osborn et al, 1961; Thrower et al, 1961; Trede et al, 1961), have been plagued with high animal mortality rates. This report, based on more than 300 animal experiments, will summarize our experience with profound hypothermia stressing (1) the acceptable animal survival rate, (2) the favorable metabolic state afforded by this technique, and (3) the protective action of profound hypothermia against even severe oxygen deprivation.

SECTION 2. METHODS

Mongrel dogs of both sexes, weighing 10 to 15 kg, were used as the experimental animal. In most instances the anesthetic agent was sodium pentobarbital, 30 mg/kg given intravenously. In some of the later experiments a combination of sodium pentothal (0.2 to 0.3 gm) and halothane (2 Bromo. - 2 Chloro, 1.1.1. - Trifluoroethane) was employed. A cuffed endotracheal tube attached to a Palmer respirator was used for control of ventilation, employing either 100% oxygen or room air.

The animals were connected to the extracorporeal system by the femoral artery. The venous return was collected from the femoral vein and the right jugular vein. The extracorporeal system consisted of a heat exchanger placed in series with the De Wall-Lillehei bubble oxygenator.

The chest was not opened except where the pulmonary artery or left auricular pressures were measured, or where the heart fibrillated and internal defibrillation was used.

Arterial and venous pressures, electrocardiogram, and fronto-occipital electroencephalogram leads were recorded in all experiments. Temperatures were taken in the mid-esophagus and rectum in all animals. The mid-esophageal temperature was used to denote the temperature of the entire animal. Under other experimental situations, temperatures were measured in the brain in one or more areas, spinal canal, and various muscles.

Procedure for perfusion has been previously described. In the majority of the experiments, ten minutes before perfusion the animals were given 30 mg/kg of quinidine hydrochloride intravenously. In 24 experiments the studies were done without quinidine; 1.5 mg/kg of heparin was injected in the vein before the insertion of the intravascular catheters. Following the perfusion the heparin was neutralized with 2 mg/kg of either hexadimethrine bromide (polybrene) or protamine sulfate.

Fifteen hundred ml of fresh heparinized blood drawn from one or two donor dogs was used to prime the pump oxygenator. This was mixed with 200 ml of normal saline solution. The donor dogs were anesthetized with ether. If after a test dose of 100 ml donor blood the experimental animal's arterial pressure dropped precipitously, the experiment was discontinued.

Flow rates of 50 ml/kg/min were used during the early part of perfusion. The temperature was rapidly brought down to 25° C. Then the flow rate of 50 ml/kg/min was reduced to between 25 and 30 ml/kg/min and kept at this rate until the animal's temperature was reduced to the desired level, usually between 7° and 10° C in the esophagus and 10° and 15° C in the rectum.

The temperature of the blood was never reduced lower than 3° C and, on rewarming, was never carried higher than 40° C.

Circulatory standstill was established by stopping the perfusion and clamping both inflow and outflow catheters. The heart usually stopped effective action when the esophageal temperature reached 25° to 20° C, and by the time 10° C was reached it was in complete standstill. After the desired period of circulatory arrest, rewarming was carried out in exactly the reverse of the cooling. When the esophageal and rectal temperatures were brought back to 35° C, the pumping was stopped. The dog was usually given 0.5 to 1 gm of calcium gluconate intravenously at the close of the perfusion period.

In certain experiments, arterial and venous blood was collected for determination of carbon dioxide content, oxygen levels, and pH. Oxygen

levels were measured on the whole blood using the method of Van Slyke and Neill (1924) or in some instances were carried out by the technique of Hickham and Frayser (1949). CO_2 content was measured according to the method of Van Slyke and Neill (1924).

The pH was read on a Beckman Model "G" pH meter under anaerobic conditions at a constant temperature of 37° C. In one series of experiments the pH level of 32 arterial samples was measured at the esophageal temperature of the dog, and then at 37° C, corrected to the same temperature, using the Rosenthal factor. The mean difference between both determinations was found to be 0.005.

In the studies where the animals were allowed to live, survival for seven days or more was considered the measure of long-term survival. The dogs were then sacrificed at intervals of seven days to six months after perfusion. Careful post mortem studies were made of any pathologic changes, with particular attention paid to the changes in the central nervous system.

SECTION 3. RESULTS

Reaction to Hypothermia and Circulatory Arrest

The animals were cooled to 7° C in approximately 40 minutes and rewarmed in the same time. As will be seen in Figure 1, the rapidity of warming decreased as the gradient between cooling fluid and blood decreased. Temperature gradients appeared in all experimental subjects. There were different rates of cooling for various organs, and the usual pattern of cooling is illustrated in Figure 1. The esophageal temperature tended to be lower than the rectal temperature, with the brain temperature in between those of the rectum and the esophagus. The muscle usually showed the highest temperature. On rewarming, the same pattern persisted, with the esophagus and brain warming rapidly and the other areas following much more slowly. It is also of interest that individual organs may show internal gradients. Previous reports have outlined these changes in the heart and in the brain (Lesage et al, 1960; Sealy et al, 1961a). In three experiments the temperatures were recorded simultaneously in the cisterna magna and in the lumbar canal. These studies were prompted by the presence of a neurologic deficit in some of our experimental animals. The cisternal temperature followed that of the esophagus until temperatures of 20° C were reached, at which time it levelled off in a manner very similar to the brain. The lumbar cord temperature followed very closely the temperature of the esophagus. However, on rewarming, the cisternal temperature rewarmed almost as rapidly as did the esophagus (Figure 2).

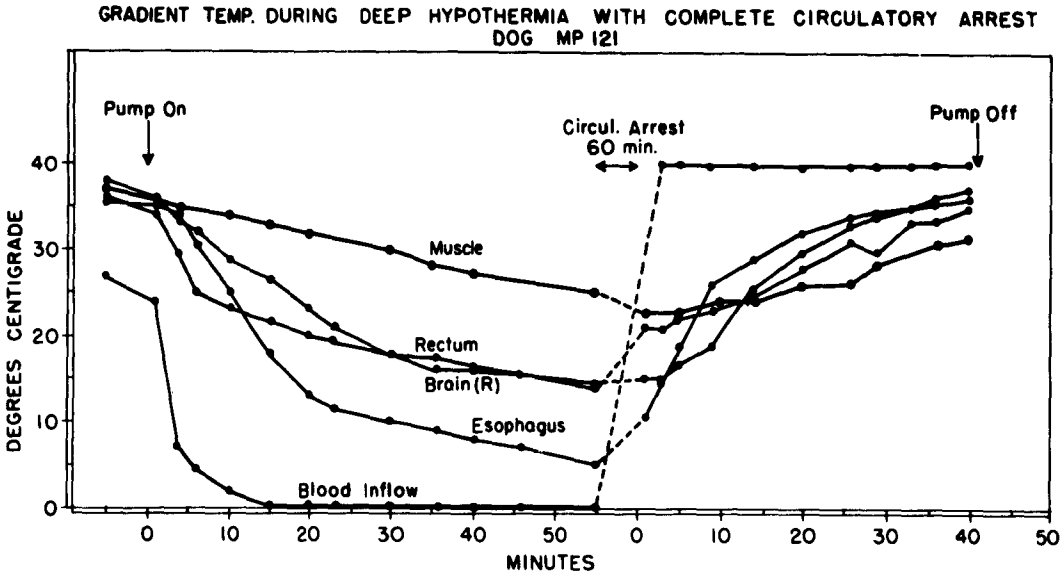

FIGURE 1. Temperature Curves During Cooling and Rewarming with Different Flow Rates and the Usual Temperature Gradient Between Esophagus, Rectum, Brain and Thigh Muscles.

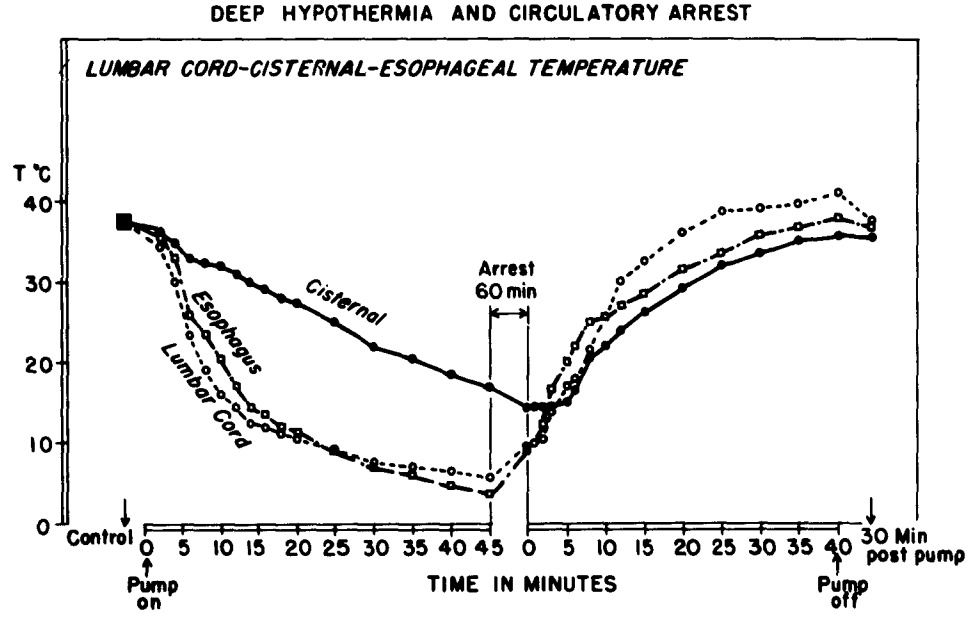

FIGURE 2. Rapid Cooling of the Lumbar Cord and Esophagus Compared to the Slow Change of the Cisternal Temperature Showing Smaller Gradients During Rewarming.

The effect of quinidine, when given rapidly intravenously in doses of 30 mg/kg just before the start of perfusion, caused the blood pressure to fall to about one-half the preinjection systolic level. As shown in Figures 3 and 4, this was increased to about two-thirds the control when the dogs were placed on extracorporeal perfusion. The pressure was then diminished as the temperature decreased (Figure 3), showing an average rate of fall to 115 mm Mercury at 37°, to 90 mm at 27°, to 55 mm at 17°, to 37 mm at 7° C. On rewarming, the arterial pressure increased in almost exactly the reverse manner that it decreased. On the same graph are shown changes in the left auricle pressure which never increased to alarmingly high levels in spite of the absence of a vent to the left side of the heart. This is explained by the marked reduction in the perfusion rate that was effected at the time the heart action became weak, usually occurring at temperatures of 25° to 20° C.

The pulmonary artery pressure decreased during cooling and increased above control values during rewarming and the post-perfusion period. This was not related to the left auricular pressure, since it did not return to normal levels when the latter returned to normal.

The action of perfusion hypothermia on the heart rate was similar to that reported by others, the rate finally diminishing to 20 beats per minute at 15° C. Complete arrest usually occurred at temperatures between 15° and 5° C. The heart action returned when the esophageal temperature reached 18° to 20° C. The pulse rate gradually increased in a reverse manner to that noted on cooling.

The arterial pressure in the dogs not given quinidine is shown in Figure 4. There was a smaller reduction in the pressure in these as compared with quinidine-treated animals. In another group where 2.5% or 5% CO_2 mixtures were used in the oxygenator, there were two with marked increase, up to 150 mm of Hg in deep hypothermia in one.

Ventricular fibrillation occurred in 30 per cent of the dogs, most frequently occurring during rewarming (Table I). Changes noted in the electrocardiogram were similar to those reported by others during hypothermia, both by external cooling and by perfusion. Myocardial function curves were obtained of the left ventricle in 11 dogs. The five dogs subjected to 30 minutes of circulatory arrest revealed little difference between the pre- and the post-arrest curves.

In six dogs subjected to 60 minutes of circulatory arrest, there was again no significant change in the function before and after the experimental period.

It is of interest that during cooling the dog absorbed a large amount of blood. This amount varied from 250 to 1000 cc or 20 to 75 cc per kg, which

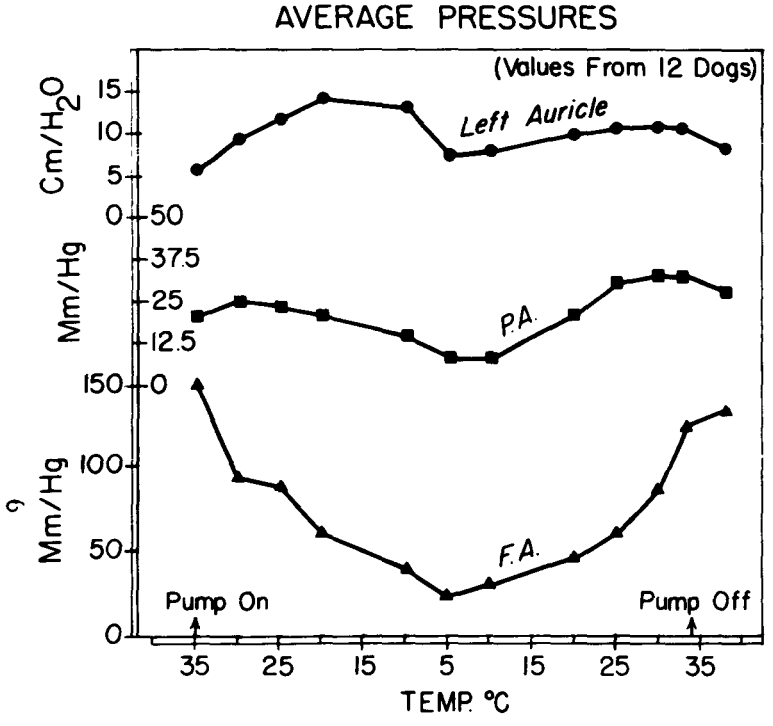

FIGURE 3.

Average Blood Pressure in the Left Auricle, Pulmonary, and Femoral Arteries Illustrating the Relatively Moderate Left Auricular Pressure During Cooling and Increased Pulmonary Pressure During Rewarming.

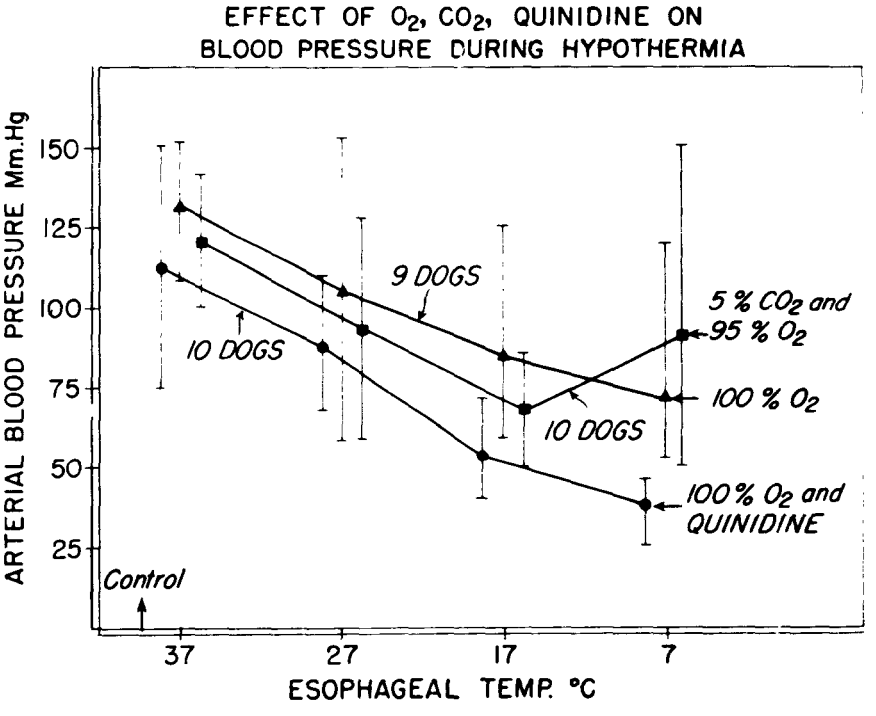

FIGURE 4.

Mean and Standard Deviation from the Mean Values of the Arterial Blood Pressure During Hypothermia Using 100% Oxygen and Quinidine in the Oxygenator, 100% Oxygen Without Quinidine, or 95% Oxygen and 5% CO_2.

represented the volume that did not return to the pump oxygenator at the end of the experiment.

Hematocrits were followed by serial estimations in eight dogs. The increases were from 4% to 17% in these experiments.

TABLE I

INSTANCE OF VENTRICULAR FIBRILLATION AFTER COMPLETE CIRCULATORY ARREST

Arrest Duration (in minutes)	Number of Dogs	Ventricular Fibrillation	Per Cent
30	6	1	16
60	65	13	20
90	14	8	57
120	6	6	100
180	3	3	100

Metabolic Data

The oxygen level in the venous blood was followed in ten dogs (Figure 5). The very high levels were noted at the lower temperature. The levels, after one hour of circulatory arrest, were obtained at two minutes and four minutes from the time of restarting the circulation. The two-minute samples were nearly always lower than the preocclusion sample, but the four-minute one tended to be high, nearly the same level noted just before circulatory occlusion.

The arterial pH levels are shown in Figure 6. A mild depression in the pH occurred at the end of one hour. The longer the period of circulatory occlusion, the more severe the post-perfusion metabolic acidosis, for the pH below 7.34 occurred in the animals that were put in arrest longer than one hour.

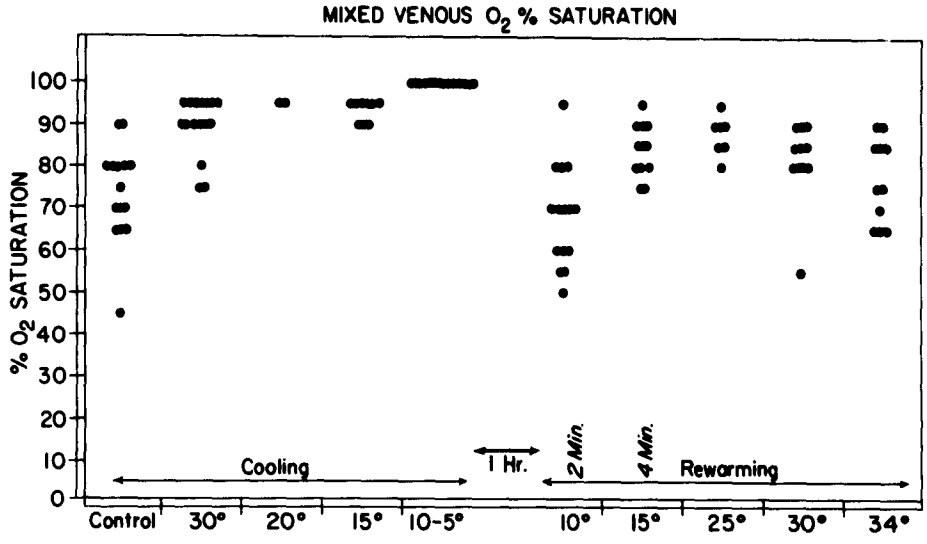

FIGURE 5.

Venous Oxygen Saturation During Cooling and Rewarming.

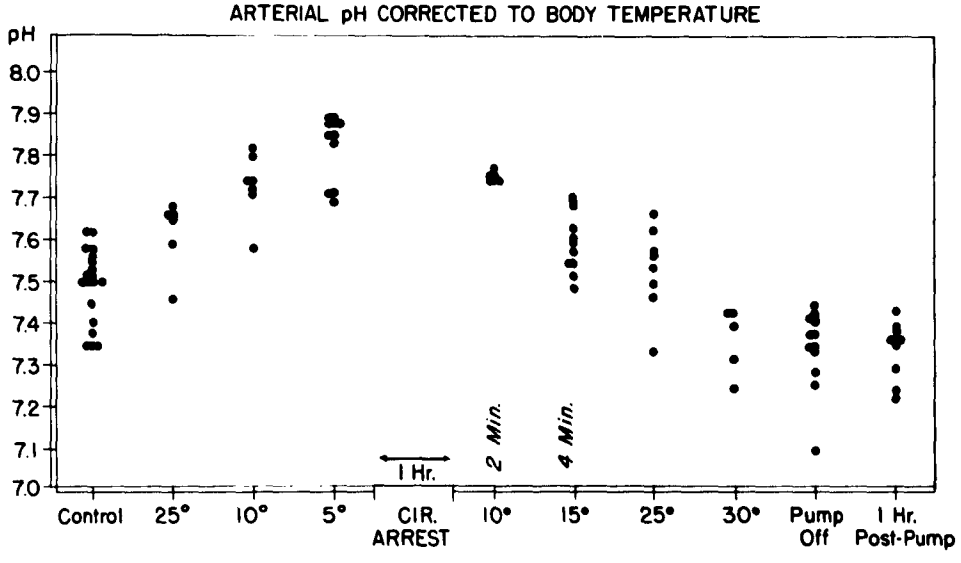

FIGURE 6.

Arterial pH Change in Perfusion Hypothermia.

Blood buffer base values were calculated in seven dogs from the CO_2 content and the pH, using the nomogram of Singer and Hastings (1948). This is shown in Table II.

TABLE II

ARTERIAL pH, BLOOD BUFFER BASE BEFORE AND AFTER HYPOTHERMIC ARREST OF 60 MINUTES

	CONTROL		END OF EXTRACORPOREAL CIRCULATION		60 MINUTES POST OP	
Dog No.	pH	BBmEq/L	pH	BBmEq/L	pH	BBmEq/L
222	7.52	44			7.20	30
220	7.50	40	7.32	33	7.18	24*
219	7.56	42	7.38	34	7.49	35
223	7.48	34	7.37	34	7.35	35
230	7.48	36	7.40	36	7.32	38.5
228	7.51	38.5	7.33	33.5	7.32	36
332	7.54	45	7.23	34	7.16	37

* This dog died during first 24 hours

Oxygen consumption studies revealed a progressive fall during hypothermia (Figure 7). To a small extent this was influenced by the flow rate as shown in Figure 8. The higher the flow rate the greater the consumption, but even at the maximum flow rates, the rate of consumption was considerably lower than the control levels.

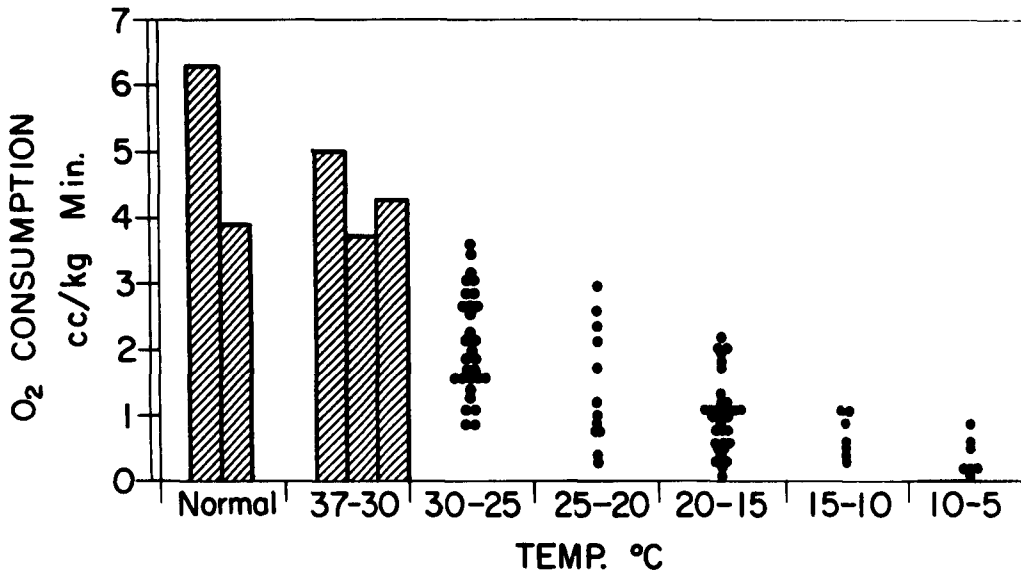

FIGURE 7. Oxygen Consumption at Different Temperatures Illustrating the Decrease with Drop in Temperature.

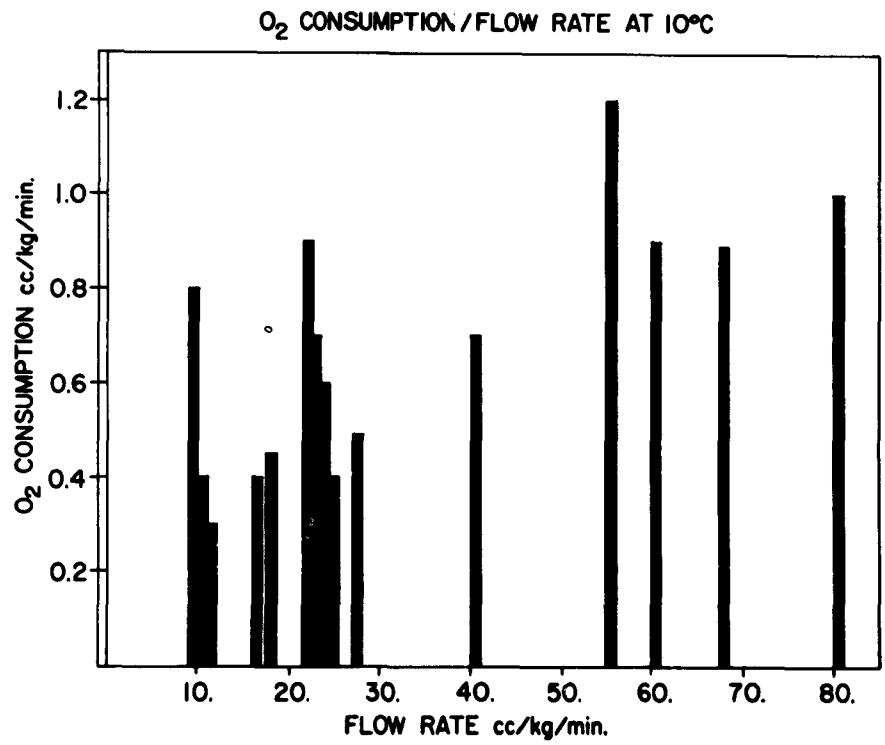

FIGURE 8. Oxygen Consumption at 10° C and Different Flow Rates Showing Rise with Increased Flow.

Survival Studies

The animals in 100 experiments were permitted to survive. The results are summarized in Table III.

TABLE III

SURVIVAL RATES IN PROFOUND HYPOTHERMIA AND CIRCULATORY ARREST

Time of Arrest	Number of Dogs	Died		Survived
		24 Hours	7 Days	
0	6	1	0	5 (85%)
30 Minutes	6	0	0	6 (100%)
60 Minutes	65	4	10	51 (78%)
90 Minutes	14	8	3	3 (21%)
120 Minutes	6	4	1	1 (17%)
180 Minutes	3	2	1	0

The Group I dogs were perfused and induced to profound hypothermia and then rewarmed. The time of profound hypothermia was from 60 to 90 minutes. One dog died; the remaining five recovered.

The Group II dogs were in circulatory arrest for 30 minutes during profound hypothermia. All the animals survived for periods longer than seven days.

The 65 dogs in Group III were in circulatory arrest for one hour at temperatures of 7° to 10° C. Fourteen dogs died, four during the first 24 hours, three in circulatory failure, and one in coma. During the second day four died from pneumonia or hemothorax and two from obvious brain damage, as shown by poor responsiveness and frequent convulsions. In the

first week one died from pneumonia, one from wound infection, one from continued coma, and the last from meningitis developing around the brain thermistor site. Fifty-one dogs, or 78 per cent, survived for more than seven days and were considered long-term survivors.

The 14 dogs in Group IV had arrest of the circulation for 90 minutes during profound hypothermia. Eleven dogs either died or were killed in the first 48 hours. Three dogs were long-term survivors. Eight of the dogs died on the day of operation due to inability to maintain circulation. Two dogs died in 48 hours, and the third at 72 hours, with severe central nervous system damage.

Of the six dogs in Group V in arrest for 120 minutes, there was only one survivor. The remaining five died either on the day of operation or in the first 24 hours from severe central nervous system damage.

There were three dogs in Group VI who were placed in arrest for 180 minutes. All of these died, with only one living for 24 hours, though he did have severe brain damage.

It is obvious from the above that the period of one hour of anoxia was the point where two events tended to occur. First, there was serious brain damage that caused the death of the animal. Second, there was damage to the entire animal in such a way that neither the heart in action nor the peripheral circulation could be maintained.

The neurologic changes related to the spinal cord were of great interest. The incidence is shown in Table IV. The spinal cord changes were manifest as mild bilateral hind leg weakness, but in severe degree it was shown by flaccid paralysis confined for the most part to the adductor muscle group with loss of control of the lower extremities. Improvement usually began in the first 24 hours. Most of the dogs recovered completely within seven days. As will be seen in Table IV, there is no correlation between either the time of circulatory occlusion, or the length of hypothermia, and the occurrence of hind quarter damage. In an effort to determine the cause, the position of the animal was changed on the table from the supine to the prone position during perfusion. This was done without improvement in four dogs. In another study, pentobarbital anesthesia was replaced by sodium pentothal and succinylcholine, or halothane; no improvement was noted. When this was done in conjunction with dilution of pump priming blood with normal saline, a decrease in the incidence of hind leg weakness, as shown in Table V, did occur. The exact significance of this finding is not clear since relationships between temperature, hematocrit, and blood viscosity were

not determined. Hematocrits in 14 dogs who did not have saline in priming blood was 41 per cent. Studies reported elsewhere which eliminated the likelihood of bubbles by reducing the high oxygen tension and removed the silicone from the system had no effect (Krasna et al, 1961).

TABLE IV

NERVOUS SYSTEM DAMAGE IN DOGS THAT SURVIVED MORE THAN 24 HOURS

Time of Arrest	Number of Dogs	CNS Damage*	Hind Quarter Weakness	No Nerve Deficit
0	5	0	3	2
30 Minutes	6	0	2	4
60 Minutes	61	8	29	24
90 Minutes	6	3	3	0
120 Minutes	2	1	1	0
180 Minutes	1	1	0	0

* Convulsions or coma

TABLE V

INCIDENCE OF HIND LIMB WEAKNESS

Anesthesia	Priming Blood	No. of Dogs Living More Than 24 Hours	No Weakness on First Day
Pentobarbital sodium	Whole Blood*	41	13 (32%)
Pentobarbital sodium	50% Blood, 50% Normal Saline (Mean hematocrit 29)	5	0 (0%)
Thiopental sodium, Halothane and Succinylcholine chloride	Whole Blood	9	2 (22%)
Thiopental sodium, Halothane and Succinylcholine chloride	50% Blood, 50% Normal Saline (Mean hematocrit 26)	11	9 (81%)

*The mean hematocrit of 14 dogs after use of whole blood for priming was found to be 41.

Pathological Studies

In 11 of the 31 dogs that died in the first 48 hours, there was congestion of the visceral structures that were drained by the portal system. The lesions noted in the portal drainage area were similar to those described by others in surgical shock, endotoxin shock, and hemorrhagic shock (Ankeney and Viles, 1960). In the heart, occasional areas of necrosis were found, while fibrosis was noted in others of longer post-perfusion survival periods. These results have been commented upon elsewhere (Sealy et al, 1961a; In press). In study of the brain and spinal cord, no consistent changes were found anywhere in either the short term or long term survivors.

SECTION 4. DISCUSSION

These laboratory studies formed the basis for the first clinical application of profound hypothermia controlled with pump oxygenator in open heart surgery (Young et al, 1959). Since the earlier reports from this laboratory, there have been many subsequent papers by others confirming the great advantages of this technique (Gerbode et al, 1961; Neville et al, 1961; Rush et al, 1961; Shields and Lewis, 1959; Urschel and Greenberg, 1960; Wilder et al, 1961). It is obvious that the maintenance of a perfect metabolic state during the cardiopulmonary by-pass is the aim of all techniques for open heart surgery. Though a reasonable state was maintained in our studies, even with prolonged periods of circulatory standstill, the ultimate measure of the safety of a new technique depends upon the mortality and morbidity of experimental animals subjected to this procedure. The dogs poor performances under all conditions of extracorporeal perfusion (high flow, low flow, cold or warm) (Cohen and Lillehei, 1954; Gordon et al, 1960; Gross et al, 1960; Juvenelle et al, 1952; Lim et al, 1961) have plagued surgeons since the pioneer work in this field by Gibbon (1937). The figures quoted in literature are difficult to summarize, but it is not unusual for even the most favorable reports to have survival rates of only 80 per cent or less (Gordon et al, 1960; Lim et al, 1961; Trede et al, 1961; Urschel and Greenberg, 1960; Wilder et al, 1961). The mortality figures herein reported are similar, even though there is the added stress of 60 minutes of circulatory standstill. Under ordinary circumstances this survival rate is prohibitively high and would preclude the use of this method on patients. This is acceptable, however, when consideration is given to the dog's peculiar reaction to blood transfusion. The difficulties encountered in perfusion with blood are outlined in detail by Maher and colleagues (1958) in a series of studies on the artificial kidney in dogs. These authors found that when 250 to 500 ml of donor blood was used to prime the system, five in 15 dogs died from shock, while 13 of the dogs had a moderately severe hypotensive reaction. Only two dogs failed to show a reaction. Where simple exchange transfusions were done, seven dogs of 17 tested showed hypotension. Four died after the exchange. This response was corrected in the kidney studies by substituting a balanced salt solution or dextran for pump priming. This phenomenon is very likely due to an anaphylactoid reaction to blood (Hamer et al, 1959). This unusual situation would not only very greatly influence the survival rate and the odd changes in the postoperative period, such as spinal cord changes, but all metabolic studies reported on the dog where the extracorporeal perfusion system was primed with donor blood. This may be the fundamental difference between the dog's and man's response to perfusion, a fact that is substantiated by wide clinical experience in several varieties of extracorporeal perfusion methods (Cooley et al, 1958; Dubost and Blondeau, 1960; Gerbode et al, 1961; Gross et al, 1960; Kirklin et al, 1960; Lillehei et al, 1957).

These experiments had as one of their aims the exclusion of any ill effect of profound hypothermia, as well as the demonstration of the beneficial effect of cold in permitting long periods of circulatory occlusion. The cold alone

was not harmful, judged both by survival rate and metabolic studies. Sixty minutes of circulatory arrest was well tolerated, but with slightly increased risk (20%). As this period of arrest (60 minutes) was approached there was a greater incidence of central nervous system damage.

When the period of circulatory standstill was extended to 90 minutes the mortality rate was much higher. The cause of death was due to either the animal's inability to maintain circulation or to serious brain damage. Beyond this period it was not possible to consistently obtain long term survivors.

Since the mortality of circulatory standstill is directly related to time, the neurologic changes have been of greatest interest. The high incidence of brain damage in long periods of circulatory standstill was not unexpected, due to the definite time relationships of anoxia and brain degeneration. On the other hand, the sporadic but high incidence of spinal cord changes have been difficult to explain. These have occurred irrespective of the length of perfusion, degree of hypothermia, duration of circulatory arrest, or incidence of brain damage. Such factors as the position of the animal during the perfusion (shifting from supine to prone), the spinal fluid pressure, the temperature gradients in the spinal cord, emboli either from oxygen bubbles or the antifoam compound were considered but have all been unrewarding (Lesage et al, 1961). The shift from a slowly metabolized barbiturate to one of shorter action combined with halothane and some hemodilution has improved to a degree our results as suggested by the earlier work of Juvenelle et al (1952). The exact reason why this change in anesthesia should be followed by improvement is not clear. The odd disparity between the findings in spinal cord and brain would suggest some factor other than hypoxia as the cause of damage to the former. On the other hand, the presence of hypoxic damage in the latter after circulatory occlusion indicates that some metabolism takes place in the brain even at low temperatures. The clinical implications of this fact are obvious.

During deep hypothermia the heart's reaction is of great importance to the cardiac surgeon, since he may need the protective action of cold for cardiac ischemia. It is obvious from our studies (Sealy et al, 1961a; 1961b), as well as in numerous reports from others (Austen et al, 1961; Ellison et al, 1960; Greenberg and Edmunds, 1961; Hufnagel et al, 1961; Kusunoki et al, 1960), that the cold alone does not damage the heart's function as measured by left ventricular function curves. An additional stress, periods of circulatory arrest of 30 minutes and 60 minutes, does not adversely affect this function. In a recent report we have outlined in detail the reaction of the heart of patients undergoing surgery during deep hypothermia as well as our experimental studies (Sealy et al, 1961b). It is obvious from the results given here, as well as from this study, that ventricular fibrillation is of no practical importance to the surgeon during open heart surgery provided provision is made to prevent left heart distention. It does not indicate serious cardiac damage, and its reversion is quite easy by means of electric shock.

Edmark (1959) and Osborn and colleagues (1961) have both commented and reported upon the fact that lowering the pH during hypothermia would, to a great degree, prevent ventricular fibrillation. Studies done in our laboratory have not confirmed this observation (Lesage et al, in preparation).

The state of the peripheral circulation during perfusion hypothermia is of interest. Since the blood viscosity is increased and the pressure head tends to be low, it is possible to postulate that a variety of adverse changes may occur in the dog due to stasis in the capillary bed. Under these circumstances, areas of increased resistance may greatly diminish flow. The work of Ebert et al (1961) has suggested that this may be so. However, our studies have indicated that during deep hypothermia the peripheral vessels are completely dilated, provided uniform cooling is present. This is in agreement with the observation of Neville, Clowes and colleagues (Oz et al, 1960). On the other hand, it is possible to have areas of unequal resistance associated with temperature gradients. For example, the slow fashion in which the muscle tends to cool has been interpreted in our studies as indication of diminished blood flow to this area. Fortunately the areas that are most sensitive to oxygen deprivation tend to have adequate flow, as shown by the cooling and warming patterns.

The vasodilating effect of quinidine may have been important in the experimental results. This drug was employed primarily to prevent ventricular fibrillation. In experiments cited, the arterial pressure was much lower even after the heart was in standstill than was noted in dogs not given quinidine. The hypertension was further enhanced by adding CO_2 to the oxygenator. It is possible that the quinidine's peripheral action may have permitted more even perfusion of the animals. The lower mortality of our experiments as compared with those of others (Juvenelle et al, 1952; Lim et al, 1961; Trede et al, 1961; Urschel and Greenberg, 1960) may be explained on this basis. Carbon dioxide may also cause more vasoconstriction, further enhancing the uneven perfusion.

In the course of our study we became concerned about the possibility of the high oxygen tension and temperature gradients working together to permit the formation of oxygen bubbles. Careful observation during all experiments has failed to reveal bubble formation in areas beyond the heat exchanger where turbulence occurs. Since the system is also coated with antifoam substance, this has also been of concern as a possible cause of focal embolic phenomenon (Thomassen et al, 1961). A series of experiments previously reported (Lesage et al, 1961) were performed to eliminate both the antifoam and the oxygen bubble danger. In these experiments cross circulation perfusion was carried out with the heat exchanger for cooling placed in the system beyond the donor dogs lungs. This permitted oxygenation of the blood to occur before cooling. There was no improvement in the survival rate, incidence of central nervous system damage, or spinal cord

damage, even when comparable temperatures and flows were employed. The pathologic study of these animals was similar to those where the regular system was employed.

The metabolic data enumerated here, as well as the work from other laboratories, are convincing proof that profound hypothermia, as used in this study, is not associated with a serious metabolic deficit. In the few experiments where post-perfusion pHs were low, this could be related to the time of circulatory arrest. It is not unexpected that periods of arrest of more than 60 minutes were accompanied by metabolic acidosis. The incidence of brain damage is consistent with this observation.

The effect of hypothermia on the oxygen metabolism and transport has been the subject of much speculation. The oldest objection to the clinical use of hypothermia is based upon the fact that cold may either adversely affect the transport of oxygen to the cell or interfere with the utilization of oxygen by the cell. Oxygen consumption studies reported, as well as the variable oxygen level in the mixed venous blood after circulatory arrest, are unquestionable evidence that oxygen can be used during deep hypothermia. This consumption rate is low. In our studies it has varied between 0.5 cc to 1 cc per kg per minute. In this regard the marked stability of oxy-hemoglobin at low temperatures has been the concern of Osborn et al (1961) and Swan (Paton et al, 1961). In other studies we have noted the steady diminution of the venous oxygen levels when this was continuously perfused in the dog by-passing the oxygenator. This is difficult to explain in view of the theoretical aspects of the problem. The greatly increased solubility of oxygen at low temperatures may partially compensate for this leftward shift of the dissociation curve of oxy-hemoglobin, but cannot explain the appreciable decrease in the venous oxygen levels in both the by-pass experiments and the post arrest determinations.

The utilization of the delivered oxygen by the cell is manifest in the favorable metabolic balance achieved in these studies. The ability to repay an oxygen debt can also be construed as evidence of active oxygen metabolism.

The solubility of carbon dioxide is also increased at profound hypothermia, but the ionization is greatly reduced. This results in a pH that is on the acidotic side when expressed at 37° C, but actually on the alkalotic side when expressed at the subject's temperature. Since this change in pH to the alkalotic side also greatly affects the dissociation curve of oxy-hemoglobin, this had led both Edmark and Osborn to use hydrochloric acid to lower pH. They have reported improvement in the oxygen utilization and decrease in the incidence of ventricular fibrillation. In spite of the theoretical benefit, our studies have not shown any change in oxygen consumption in dogs by decreasing the pH with both carbon dioxide and hydrochloric acid (Lesage et al, In preparation).

The maximum amount of blood flow needed during deep hypothermia has been studied by Neville and Clowes (Kameya et al, 1960). Their observation, which we have confirmed, shows that oxygen is utilized in increasing amounts in flow rates up to 50 to 60 cc per kg per minute. Above this level there is no significant increase in oxygen consumption with increase in rate. In clinical application where the situation demands, our studies have shown that less than optimum flow rates are consistent with a satisfactory metabolic state due to the protective action of the hypothermia.

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3. Dogs
4. Heart
5. Surgery
6. Blood Circulation
7. Obstruction (Physiology)
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